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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/694,207	10/27/2003	Ekambar R. Kandimalla	HYB-005US7	3842

7590 12/16/2008

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EXAMINER	
BLANCHARD, DAVID J	
ART UNIT	PAPER NUMBER
1643	
MAIL DATE	DELIVERY MODE
12/16/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	Application No.	Applicant(s)	
	10/694,207	KANDIMALLA ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 04 December 2008 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).

5. ☐ Applicant's reply has overcome the following rejection(s): _____.

6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *26,28,29,34 and 35*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).

9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).

10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.

12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____

13. ☐ Other: _____.

/David J Blanchard/
Primary Examiner, Art Unit 1643

Continuation of 11. does NOT place the application in condition for allowance because:
The rejection of claims 26, 28-29 and 34-35 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The response filed 12/4/2008 states that applcants' contribution is the replacement of cystine in a CpG dinucleotide of any such immunostimulatory CpG-containing oligonucleotide by 5-hydroxycytosine, 5-hydroxymethylcytosine, N4-alkylcytosine and 4-thiouracil would not diminish and may enhance the immunostimulatory activity of any such oligonucleotide. Applicants' arguments have been fulyl considered but are not found persuasive. As stated in the previous Office Action, the examiner maintains that the written description of the present application only sets forth a single immunostimulatory oligonucleotide (i.e., 5'-CTATCTGACGTTCTCTGT-3') comprising the formula C*pG, wherein C* is 5-hydroxycytosine, 5-hydroxymethylcytosine or N4-ethylcytosine that stimulates an immune response, however, the claims encompass thousands or millions of immunostimulatory oligonucleotides that differ in length and sequence, and which generate an immune response in a patient or treat cancer in a patient. The structures of the immunostimulatory oligonucleotides comprising the formula C*pG, wherein C* is selected from 5-hydroxycytosine, 5-hydroxymethylcytosine, N4-alkylcytosine and 4-thiouracil that generate an immune response in a patient or treat caner in a patient are not known and the genus is inclusive to a variety of subgenera having disparate structures and functions. Thus, the instant disclosure does not provide sufficient written description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus or various subgenera of immunostimulatory oligonucleotides comprising the formula C*pG, wherein C* is selected from 5-hydroxycytosine, 5-hydroxymethylcytosine, N4-alkylcytosine and 4-thiouracil that generate an immune response in a patient or treat caner in a patient. See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406. For example, Figures 22, 23 and 26 as pointed to by applicant demonstrate that the immunostimulatory oligonucleotide 5'-CTATCTGACGTTCTCTGT-3' in the absence of C* elicits an immune response that is equal to or greater than the immune response elicited when C* is present and selected from 5-hydroxycytosine, 5-hydroxymethylcytosine and 4-thiouracil. The instant application does not provide a correlation between the common structure C*pG, wherein C* is selected from 5-hydroxycytosine, 5-hydroxymethylcytosine, N4-alkylcytosine and 4-thiouracil and a common function, i.e., generate an immune response in a patient or treat caner in a patient. Again, the specification discloses that a CpG oligonucleotide comprising the cytosine analogs, particularly 5-hydroxycytosine or N4-ethylcytosine, can be modulated significantly by incorporating appropriate chemical modifications in the 5'-flanking sequence, suggesting that these cytosine analogs in a CpG-motif are recognized as part of an immunostimulatory motif. The specification also discloses that when the cytosine of the CpG-motif is replaced with uracil, no immunostimulatory activity was observed. Similarly, the relevant CpG immunostimulatory oligonucleotide art (e.g., Vollmer et al, Verthelyi et al and Dittmer et al, all of record) teaches that the length, sequence and backbone modification can alter the immunostimulatory properties of CpG oligonucleotides. Thus, one of skill in the art could not predict the operability of any other species of immunostimulatory oligonucleotides comprising an immunostimulatory dinucleotide having the formula C*pG, wherein C* is selected from 5-hydroxycytosine, 5-hydroxymethylcytosine, N4-alkylcytosine and 4-thiouracil other than those disclosed. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]. " See Enzo Biochem, 323 F.3d at 966, 63 USPQ2d at 1615; Noelle v. Lederman, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004)("[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated."). "A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when … the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed."

Applicant also argues that one skilled in the art would simply look to the previously existing immunostimulatory oligonucleotides to recognize whether any particular embodiment of the claimed invention would be operable. Applicant asserts that if a given CpG-containing oligonucleotide selected from the prior art is immunostimulatory, its sequence will remain immunostimulatory with Applicants' modification, if it is not, it will likely continue to not be operative with Applicants' modification. Applcants' arguments have been fully considered but are not found persuasive. The issue is not whether one skilled in the art could make and use the claimed immunostimulatory oligonucleotides comprising the formula C*pG, wherein C* is selected from 5-hydroxycytosine, 5-hydroxymethylcytosine, N4-alkylcytosine and 4-thiouracil that generate an immune response in a patient or treat cancer in a patient, the issue is whether the written description of the instant application adequately conveys that applicants' were in possession of the claimed invention. As discussed in detail above, one skilled in the art would not conclude that applicant's were in possession of the claimed invention. Applicant is reminded that the written description requirement is separate and distinct from the enablement requirement. In re Barker, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978); Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991) (While acknowledging that some of its cases concerning the written description requirement and the enablement requirement are confusing, the Federal Circuit reaffirmed that under 35 U.S.C. 112, first paragraph, the written description requirement is separate and distinct from the enablement requirement and gave an example thereof.). An invention may be described without the disclosure being enabling (e.g., a chemical compound for which there is no disclosed or apparent method of making), and a disclosure could be enabling without describing the invention (e.g., a specification describing a method of making and using a paint composition made of functionally defined ingredients within broad ranges would be enabling for formulations falling within the description but would not describe any specific formulation). See MPEP 2161.
Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991), with respect to the first paragraph of §112 the severability of its "written description" provision from its enablement ("make and use") provision was recognized by this court's predecessor, the Court of Customs and Patent Appeals, as early as In re Ruschig, 379 F.2d 990, 154 USPQ 118 (CCPA 1967). Although the appellants in that case had

presumed that the rejection appealed from was based on the enablement requirement of §112, id. at 995, 154 USPQ at 123, the court disagreed: the question is not whether [one skilled in the art] would be so enabled but whether the specification discloses the compound to him, specifically, as something appellants actually invented. ... If [the rejection is] based on section 112, it is on the requirement thereof that "The specification shall contain a written description of the invention * * *." (Emphasis ours.) Id. at 995-96, 154 USPQ at 123 (first emphasis added). The issue, as the court saw it, was one of fact: "Does the specification convey clearly to those skilled in the art, to whom it is addressed, in any way, the information that appellants invented that specific compound [claimed]?" Id. at 996, 154 USPQ at 123. In a 1971 case again involving chemical subject matter, the court expressly stated that "it is possible for a specification to enable the practice of an invention as broadly as it is claimed, and still not describe that invention." In re DiLeone, 436 F.2d 1404, 1405, 168 USPQ 592, 593 (CCPA 1971) (emphasis added). As an example, the court posited the situation "where the specification discusses only compound A and contains no broadening language of any kind. This might very well enable one skilled in the art to make and use compounds B and C; yet the class consisting of A, B and C has not been described." Id. at 1405 n.1, 168 USPQ 593 n.1 (emphases in original). See also In re Ahlbrecht, 435 F.2d 908, 911, 168 USPQ 293, 296 (CCPA 1971) (although disclosure of parent application may have enabled production of claimed esters having 2-12 methylene groups, it only described esters having 3-12 methylene groups).
For these reasosn and those already of record, the rejections is maintained.